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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,152	07/23/2003	David B. Agus	67789-19	1369

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

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10/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,152	AGUS, DAVID B.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-12,15-23,25,29,31,57-64,67,68,71-78,81,82 and 85-88* is/are pending in the application.

4a) Of the above claim(s) *10,21,29,31,67,68,81 and 82* is/are withdrawn from consideration.

5)☒ Claim(s) *23,25,63,64,77 and 78* is/are allowed.

6)☒ Claim(s) *1,4-9,11,12,15-20,22,57-62,71-76 and 85-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 7/25/2007 and Information Disclosure Statement filed 8/31/2007 have been received and entered into the application. Accordingly, claims 12, 60, 75, and 87 have been amended and claims 26, 28, 32, 34, 65, 66, 69, 70, 79, 80, 83, and 84 have been cancelled.

Claims 1, 4-12, 15-23, 25, 29, 31, 57-64, 67-68, 71-78, 81-82, and 85-88 are presented for examination. Claims 10, 21, 29, 31, 67-68, and 81-82 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Accordingly, claims 1, 4-9, 11-12, 15-20, 22-23, 25, 57-64, 71-78, and 85-88 are presently under examination and are the subject of this Office Action.

The Information Disclosure Statements filed 7/25/2007 and 10/10/2007 are both blank. Accordingly, the Examiner has not considered the submitted reference.

Applicants' arguments, filed 7/25/2007, have been fully considered and are deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-9, 11-12, 15-20, 22, 57-62, 71-76, and 85-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating androgen-independent prostate cancer with raloxifene, does not reasonably provide enablement for treating androgen-independent cancer with the full scope of compounds recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

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[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

The nature of the invention: The invention relates to methods of inhibiting tumor growth of androgen-independent prostate cancer in a mammal comprising administering a compound of the formula recited in the claims. The compounds recited in the claims include the estrogen-receptor modulator (SERM), raloxifene, as well as derivatives and prodrugs of raloxifene.

Relative skill of those in the art: The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

State and predictability of the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). The treatment of androgen-independent prostate cancer (AIPC) is much more unpredictable than the treatment of androgen-dependent prostate cancer (ADPC). In fact, drugs used to treat ADPC are generally not effective in treating AIPC. For example, Applicant teaches at page 2, lines 6-18 of the instant specification that:

> "Androgen-independent prostate cancer (also called hormone refractory prostate cancer) does not depend on androgens for its growth; as a result, hormone ablative therapy has little effect on it. Even therapies that are highly effective at treating androgen-dependent cancers have been shown to be ineffective when applied to patients with androgen-independent cancer.
>
> Androgen-independent cancer is difficult to treat. One can decrease the size of prostate inflammation associated with the cancer, such as with corticosteroids and other anti-inflammatory agents, but such treatment has no effect on the cancer itself. For

> this reason, a basic medical text still teaches that "There is no standard therapy for hormone refractory prostate cancer." M. H. Beers and R. Berkow, eds., Merck Manual of Diagnosis and Therapy, 1658 (1999). According to this text, cytotoxic and biologic agents "are being investigated," but "their superiority to corticosteroids alone has not been proved." (emphasis added)

It is apparent that the treatment of AIPC is difficult and unpredictable in the sense that chemotherapeutic agents useful to treat androgen-dependent prostate cancer would not be expected, a priori, to be effective in treating androgen-independent prostate cancer. Further, raloxifene, as encompassed by the instant claims and explicitly claimed in claim 23, is an antiestrogen. Antiestrogens (*e.g.*, tamoxifen) "have exhibited no effect on androgen-independent prostate cancer in several previous clinical trials" (page 5, line 20 to page 6, line 1 of instant specification).

The breadth of the claims: The claims vary in breadth; some (such as claim 1) vary broadly, reciting the treatment of tumors of AIPC with a broad genus of compounds. Others, such as claims 23, are narrower, reciting a specific species of the claimed genus of compounds. All, however, are extremely broad insofar as they disclose the general treatment of tumors of AIPC with the same compounds.

The amount of direction or guidance provided and the presence or absence of working examples: The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all of the various tumors claimed, particularly in humans. The direction concerning treating cancer is found in the specification at pages 11-24, which provides cellular assays, *in vivo* assays, and a

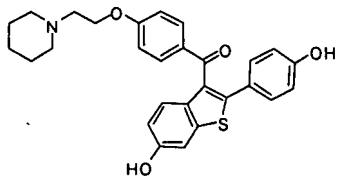
clinical trial of raloxifene in the treatment of AIPC. No compounds of the invention, other than raloxifene, were tested in these assays. Applicant describes formulations at pages 9-10. Doses required to practice their invention are described at pages 8-9. In general, doses of between 10 mg and 300 mg per day are suggested. Since only one compound of the invention has ever been used to treat androgen-independent prostate cancer, how is the skilled physician to know what dose to use for each of these structurally diverse compounds? Are the identical doses to be used for each of these thousands of possible compounds? Further, claim 12 recites prodrugs of the claimed compounds, wherein at least one of the substituents is "metabolically processed" after administration to convert the prodrug into a pharmaceutical compound effective to treat AIPC. However, the metabolism of any given compound cannot be predicted *a priori*, especially when the compounds can be administered orally, intravenously, or *via* intramuscular injection. As such, it is left to the skilled artisan to figure out, with no guidance from the specification, exactly which of the claimed prodrugs will be metabolically processed in a manner that results in a pharmaceutically effective metabolite.

The quantity of experimentation necessary: Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds, other than raloxifene, could be predictably used as a treatment for androgen-independent prostate cancer as inferred in the claims and contemplated by the specification.

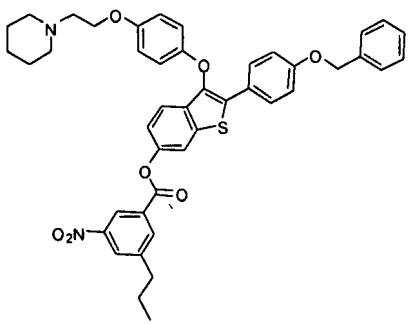
Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is

granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

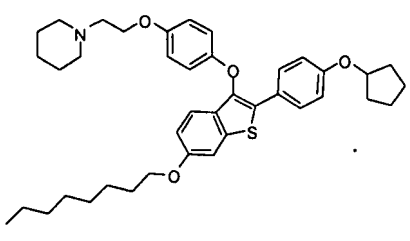
In the instant case, Applicant has presented a general idea that because raloxifene is effective to treat androgen-independent prostate cancer, then all of the derivatives and prodrugs as instantly claimed must therefore, *a priori*, be useful in the treatment of androgen-independent prostate cancer. However, the claims encompass thousands of compounds having a plethora of chemically and biologically distinct substituents. Applicant tested one commercially available compound (raloxifene). Raloxifene is a relatively simple compound that is a known antiestrogen that is used clinically in to prevent osteoporosis in postmenopausal women and also to reduce the incidence of breast cancer in certain high risk groups of females. Whether any of the other compounds encompassed by the claims have the same activity as raloxifene cannot be predicted a priori. For example, the claims encompass administering the following structurally diverse compounds.



Raloxifene



Compound A



Compound B

Compounds A and B are hypothetical compounds that are encompassed by the claims. These compounds, and compounds like them, have not been synthesized or tested. One skilled in the art would not reasonably expect that Compound A or Compound B would have similar activity to raloxifene. Given the extremely diverse compounds encompassed by the claims and the limited examples provided in the specification, the skilled artisan cannot predict what structural features are important for efficacy in the treatment of AIPC.

Determining if any particular claimed compound would be an effective treatment of AIPC would require synthesis of the compound (with no guidance in the specification), formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicant. As noted *supra*, antiestrogens are not generally known to be effective in the treatment of AIPC. As such, the discovery that the antiestrogen raloxifene is effective is unexpected and not predictive that derivatives and prodrugs of raloxifene will also be effective.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Allowable Subject Matter

Claims 23, 25, 63, 64, 77, and 78 are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

October 13, 2007

10/13/07
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SUPERVISORY PATENT EXAMINER